CEPHALIC INFLUENCES ON HUMAN GASTRIC ACID SECRETION AND THEIR VOLUNTARY CONTROL THROUGH FEEDBACK TRAINING

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Cephalic Influences on Human Gastric Acid Secretion and their Voluntary Control Through Feedback Training.

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Can human gastric secretory activity be altered by direct voluntary control? The problem was attacked in three stages: 1) the development of a technique for continuous observation of gastric acid secretory response in the intact normal human, 2) precise observation of the characteristics of involuntary responses to excitatory and inhibitory cephalic stimuli, and 3) observations of the effects of voluntary efforts with appropriate signal feedback and reinforcement.

Three human subjects, two males and one female, and all between 20 and 30 years of age, participated in all three stages. Overnight fasting preceded each observation.

I. Development of the technique for continuous observation. By titrating intragastrically continuously, an analog to the secretory rate appears in the rate at which neutralizing agent is demanded to maintain an end point. 0.1N Sodium Bicarbonate was infused by a Radiometer pH-stat assembly. (Model TTT II, ABU1a). pH was registered with the Beckman intragastric electrode (Model 39042), with an agar-suspended bridge to the calomel reference. Mixing was promoted by continuous infusion of water with a Sigmamotor peristaltic pump. Subjects reclined at approximately 65° from horizontal in a lounge chair in a sound and odor shielded chamber. A 45 minute equilibration period

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preceded all data collection. The recorded basal acid secretory rate was 12.3 mEq/hr. or .205 mEq/min. with a standard error of 0.043 mEq/min. from the linear slope. Day to day fluctuations in a secretory level were substantial.

II. *Observations of involuntary acid secretory responses* to cephalic stimuli with antrum neutralized. An excitatory and an inhibitory stimulus were presented in randomized order to each subject on separate days. The excitatory stimulus was a light warm breakfast of the subject's own choosing attractively served. The inhibitory stimulus was warmed canine feces served in an identical manner. The stimuli were concealed beneath a metal dome until the precise moment of presentation. Exposure lasted for five minutes.

A bi-phasic excitatory response appeared with an average latency of 2.2 minutes. The first phase peaked at 8.8 minutes, averaged .223 mEq/min. and lasted 16.1 minutes. The second phase began 18 minutes after stimulation, peaked at 23 minutes, and continued beyond the 45 minute observation period. Since pre-stimulus levels averaged 0.083 mEq/min., these peaks represented 270% and 290% increases respectively.

The inhibitory response was also bi-phasic. After 30-45 seconds a 50% reduction in acid secretory rate occurred, with the nadir at 6 minutes and average duration 13 minutes. After 18.5 minutes a rebound of approximately 9 minutes was observed and reached 200% of the pre-stimulus level. One subject showed no inhibitory response.

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III. Observations of voluntary responses to reinforcement with information feedback. Each subject was given four days of operant trials with three 15 minute trials each day. First acid secretory decrease was reinforced with token minute-to-minute money reward. If a criterion of 100% increase over a 15 minute baseline was achieved on a trial, a $10 bonus was awarded. When this criterion was reached, voluntary increases would be reinforced on succeeding days. Momentary pH level was presented visibly with the meter face, and rate of titrant flow was signaled by an analog click.

Eighteen of 30 trials to inhibit acid were successful. A training effect was apparent within days, but not from day to day. The degree of control was typically about 25%. One subject exhibited 100% inhibition for more than 20 minutes on the second day. The group's results were very highly significant (p<.001).

The one subject who reached the criterion began efforts at voluntary increase the following day. Again, token rewards for each minute were announced, and a $10 bonus offered for achieving 100% increase. On the first three trials, this subject achieved increases of 100, 50 and 109% above baseline.

The inference was drawn that with appropriate reinforcement and prompt feedback of information on gastric acid secretory activity, some degree of voluntary control over acid secretory activity appeared attainable in a short time. The degree varied greatly between subjects, but all three exhibited some degree of control in only four days of training.

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Chapter 1

INTRODUCTION

Man's understanding of psychosomatic relationships has been evolving for many centuries, with rapid advances in the last hundred years. The effect of his conscious processes on the function of internal organs has received particular attention recently. A number of factors contributed to this development: technological advances provided more sensitive observation of internal processes; research suggested that man may be able to exercise voluntary control over bodily functions traditionally considered involuntary; potential applications in psychosomatic medicine justified substantial efforts to corroborate and expand the positive finding~~s~~ of the preliminary research, giving rise to a whole new interest area in psychology called Biofeedback.

The language of Biofeedback is borrowed largely from the psychology of learning. Behavioral scientists have developed a large repertoire of techniques and specific terminology to describe them. A learning process is described in terms of observable operations. Conditioning is the process of pairing a stimulus with a response repeatedly to increase the likelihood of the occurrence of that response. Two general types of conditioning are classical and operant. Pavlov's famous experiments were in the classical paradigm: a neutral stimulus (a bell) was presented along with an unconditioned eliciting stimulus (meat paste) to an organism. Only the latter elicited the response (salivation), but repeated paired presentations of the two established

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an association between them as evidenced by the fact that the bell alone would elicit a response similar to the one to food.

Operant conditioning proceeds in a different manner: the unconditioned stimulus (often called a reward) is presented only after the desired response occurs. A set of experimental circumstances under which the reward will follow may also be specified. These are called reinforcement contingencies. After repeated rewards, the frequency of occurrence of the desired response increases. Reward contingencies take on cue properties, which increase the likelihood of the response. For example, if Pavlov gave the dog food only if it increased salivation, a pattern of increased salivation would ensue. If he rewarded salivation only if it occurred following the ringing of a bell, the bell itself would become a cue for salivation. The activity of the organism operating on the environment is called the operant. Operant behavior is instrumental in securing the reward. Thus the name operant, or instrumental conditioning.

A simple way to characterize the distinction is: in classical conditioning the behavior is elicited by the reward; in instrumental conditioning the reward follows once the behavior is emitted.

The research on instrumental conditioning focuses on easily observable gross skeletal behaviors. Within the last two decades there has been a growing interest in applying this technique to more subtle behaviors, and those innervated by the autonomic nervous system (ANS). This research challenged the traditional notion that autonomic behavior, by definition, is involuntary and cannot be emitted.

A large body of research indicates that processes mediated by the ANS (called autonomic processes) may be modified by operant con-

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ditioning. In 1958 Lisina discovered that human subjects learned to escape electrical shock by dilating blood vessels in their forearms. These subjects had undergone 80 repetitions of electric shock, which produced vasoconstriction. The experimenter then let them watch their plethysmographic records while being shocked, so they discovered the relationship between their own vasomotor activity and the occurrence of shock. Within a few sessions thereafter subjects began to exhibit vasodilation more and more frequently, until this was the predominant response.

In this experiment the reward which followed the appropriate response was escaping the shock, a paradigm called negative reinforcement. In operant conditioning, the behavior would ordinarily be easily observed by both the experimenter and the subject. In this case sensitive transducers with amplifiers and displays were required. The criterion and mechanism for reward was automated, so that reinforcement could follow an appropriate response almost as soon as it was detected. The reward must follow the correct response promptly for learning to take place. If intervening responses occur, the organism may learn the wrong response, or nothing at all. Both accurate knowledge of results and effective reward contribute to learning. The first was provided by the plethysmographic display when related to the second, the pattern of shock.

A number of studies since that time have pointed to the conclusion that autonomic processes are similarly conditionable, even when skeletal activity is blocked by curare (Miller & Di Cara, 1967; Di Cara & Miller, 1968). When Miller (1972) reported that successive replications of his early work on learned control of heart rate in curarized

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rats showed gradually decreasing magnitudes of change, no explanation for the decreases could be found. While the replication anomaly remains, other evidence for successful ANS conditioning has appeared (Engel & Bleecker, 1974; Roberts, Schuler, Bacon, & Zimmerman, 1974). Successful applications to clinical entities involving autonomic regulation have been reported with increasing frequency (e.g., Weiss & Engel, 1971; Harris, Gilham, Findley, & Brady, 1973; Wells, 1973; Bleecker & Engel, 1973; Edder, Ruiz, Dealster, & Dillenkoffer, 1973; Rosen, 1973). While the theoretical issue of direct conditionability is still alive, the possibility of successfully applying instrumental techniques to ANS mediated processes is no longer in question (Shapiro & Schwartz, 1972).

Human Gastric Acid Secretion

Gastric acid secretion, a process partially regulated by the ANS, has only recently received attention as a candidate for instrumental conditioning. Since the subject of gastric physiology is complex and not usually familiar to behavioral scientists, a brief review of present knowledge may be helpful. By convention, mammalian gastric secretion is described in terms of three levels of influence: cephalic, gastric, and intestinal. The cephalic influence is mediated through the vagus nerve. The sight and smell of food, for example, triggers cortical and limbic responses which are relayed through the vagus to the acid-secreting cells in the fundus and corpus and gastrin-secreting cells concentrated in the pyloric area of the stomach (Figure 1.1). The acid is secreted from the gastric pits into the stomach lumen. Gastrin is released into the mucosal vascular system. The circulated gastrin acts synergistically with acetylcholine at the site of stimulation of the acid-secreting cells to promote further secretion

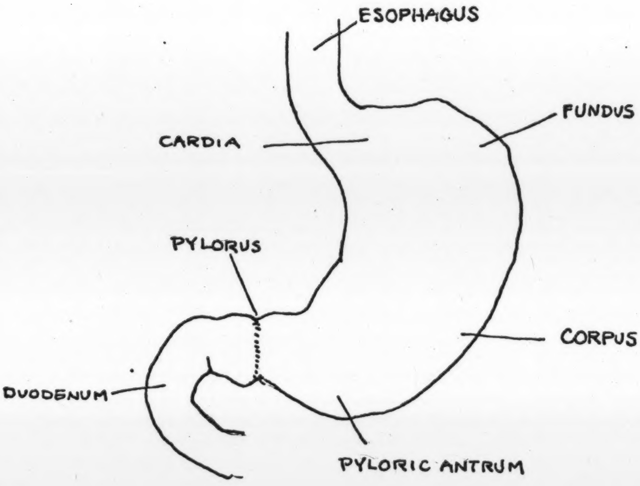

Figure 1.1 Gross anatomy of the human stomach.

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(Brooks, 1970). The brain may also influence secretion indirectly through vasoconstrictive catecholamines (Smith & Brooks, 1967).

At the gastric level, control is primarily through local reflexes. The presence of food and other substances in the stomach or simply distention of the stomach area stimulates secretion via vagovagal reflexes (Brooks, 1970). Of particular importance for instrumental modification of gastric secretory response is the autoregulation of acid by local pH sensors and reflexes. Intra-antral pH exerts a nearly linear inhibitory effect on vagal release of gastrin between 3.5 and 1.0. Above pH 3.5 there can be maximal secretory response; below approximately 1.0 there is complete inhibition. At pH 2.0, the reduction is about 30% (Anderson & Olbe, 1964). The pH level does not itself evoke the release of gastrin, but grades the response of the antral gastrin-releasing mechanism to vagal stimulation. This in turn stimulates acid release and facilitates cholinergic activation of the acid secreting cells. In order to observe maximal response to cephalic activity, antral pH must be maintained at or above 3.5. In dogs, resting pH is close to neutral (pH 7), but in man, it is commonly between 1.5 and 2.0 after overnight fasting.

At the intestinal level, hormonal mechanisms act to inhibit acid secretion in response to acid in the duodenal bulb via secretin and in response to fat in the intestine via enterogastrone.

Any attempt to modify the secretory rate by voluntary control at the cephalic level must take into account the chain of reactions at the other levels, as well.

The research described in this paper explores the question whether the gastric acid secretory system is responsive to instrumental

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learning. More immediately it seeks to establish a feasible technique for asking such a question, and to provide basic information about certain characteristics of the response system observed. The research can be described as three studies:

(1) the development of a technique for continuous observation of gastric acid secretory response in the intact normal human;

(2) observations of the characteristics of the acid secretory response to excitatory and inhibitory visual-olfactory stimuli; and

(3) observations of the effects of information feedback and reinforcement on the acid secretory response system.

Each of these studies will comprise a chapter. A final chapter will summarize the series of studies, noting their limitations, drawing tentative conclusions, and suggesting further research.

Chapter 2

A TECHNIQUE FOR CONTINUOUS OBSERVATION OF GASTRIC ACID SECRETION

Introduction

The proposed research demands a sensitive, fast technique to provide acid secretory information. The broad constraints of this technique are inherent in the biofeedback paradigm; the specific parameters can be projected from previous research in gastric psychophysiology. The general specifications of a biofeedback technique suitable to gastric acid secretory response will be outlined and will serve as a framework for a review of the techniques previously reported and their results. The technique employed in this study will then be explained and some baseline results presented.

Requirements of a Biofeedback System

In order to gain control over a physiological event, one must first become aware of the presence or absence of that event, or the level of that event, or both. The system for monitoring that event must be sensitive, accurate, and relatively free of artifact (Budzynski, 1973). If an investigator seeks to enable a subject to modify a response in one way or another by administering a reward, he must decide whether each of the responses the subject emits are to be rewarded. Before the occurrence of another such response, he must indicate his decision to the subject by the reward or non-reward (Engel & Hansen, 1966). The observation-decision-reward process may not exceed the time it takes to

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initiate a subsequent response, lest the subject attach the reward to the wrong behavior, and learn the wrong thing. In short, both knowledge of results and reward must be "on line."

The sort of information that is fed back must also be meaningful. Raw physiological data usually require analysis and interpretation before being returned to the subject in a form immediately obvious and clearly related to the performance desired.

Requirements of a Gastric Acid Secretory Response Biofeedback System

The characteristics of gastric acid secretory activity suggest specific requirements for successful biofeedback modification. Normal resting secretion of gastric acid occurs at the rate of approximately 2.5 mEq/hr., or less than 0.05 mEq/min (Grossman, 1963). If observations are to take place in intervals of one minute, the measurement must be sensitive to changes of 0.01 ml or less. Error tolerance of 10% would then require accuracy to 0.001 ml.

The speed of the response determines how fast this information must be returned to the subject. When the response is part of a continuous process, as in this case, it is not clear what arbitrary segment ought to be considered a discrete response. The latency of a discernible change in the response can be used as a guide. But the latency of cephalic response is not precisely known, either.

Janowitz and his colleagues reported the effects of different types of meal on volume of acid secreted by a woman with a total esophageal block and fistulated stomach. The latency of the response was less than five minutes and perhaps less than two (Janowitz, Hollander, Orringer, Levy, Winkelstein, Kaufman & Margolin, 1950). Gerver (reported in Bechterev, 1911) explored the effect of cortical stimulation on canine gastric secretion. He found an area of the anterior sigmoid gyrus which, when stimulated, caused secretion of gastric juice within two to five minutes. Klopper (1954) replicated this finding in cats and noted a drop in gastric pH from pH 4-5 down to 2 within 15 seconds. Physiological considerations make it very unlikely that a latency as short as a fraction of a minute could occur. For an empirical answer to the question of latency, however, the appropriate time range would appear from these data to be anywhere from 0.25 to 2.5 minutes.

Since acid secretion is normally a continuous process, the level of the response rather than its presence or absence is the target of modification. The level can range from 0 to 50 mEq/hr. depending on the person and stimulus (Card & Marks, 1960). In an individual, the level varies spontaneously from day to day, moment to moment by as much as 25%. The variability is less than 10% for maximal acid secretion in response to pharmacologic stimulation. Variability represents a statistical problem, since changes must be large and consistent to be seen against the background of spontaneous fluctuation. Variability, on the other hand, is a prerequisite for operant modification of behavior. For biofeedback applications, the decision to reward need not include a calculation of statistical significance: the reward criterion can be simply an increase or decrease of rate in some epoch compared to some other, or some absolute standard. Any external display directly expressing the rate of secretion continuously would provide a subject with the means to acquire awareness of the physiological process of interest. Comparisons of the rate averaged over a number of samples would reduce some of the variability due to measuring technique and very brief fluctuations. Since most subjects are at home with linear mathematical expressions, a simple linear expression of acid secretory rate would be the natural starting point for feedback.

Methods of Monitoring Gastric Acid Secretion

There are a number of methods for assessing acid secretion in the intact human stomach. These vary in sensitivity, accuracy, speed, and meaningfulness, and therefore applicability for biofeedback.

The traditional method used in clinical assessment is aspiration of the stomach contents. Samples are collected in 15 minute intervals, but for research purposes may be drawn continuously (Welgan, 1974; Moore & Schenkenberg, 1974). This technique allows for in vitro titration of the contents yielding measures of volume and concentration of acid and other juices over time. Acid secretion is usually expressed as milliequivalents of total titratable acid over some specified time. Sensitivity to the second decimal place (0.01 mEq) can be achieved, with 90% accuracy or better. Welgan assayed 15 minute samples*, and Moore & Schenkenberg 12 minute samples. The speed demanded by biofeedback would require that samples be collected over much smaller periods of time.

To determine whether one minute samples could be analyzed with comparable sensitivity and accuracy, I conducted an experiment. A subject with extensive experience in swallowing electrodes and tubes was recruited. After overnight fasting he was placed on his left side on a cot in a small sound-shielded dimly lit room. A standard 16F nasogastric tube was introduced orally up to the 55 cm mark. The tube was then connected to a longer section (100 cm) of polyethylene tubing of similar diameter (0.6 cm) which passed through a peristaltic pump (Sigma-motor T65) with continuously variable speed. A 200 ml beaker and a rack of twenty 12 cc calibrated test tubes were placed in a 37° C. water bath.

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*The feedback in Welgan's experiment was not acid secretion itself, but pH of the gastric contents passing through the collection tube.

When the subject was comfortable and habituated to the experimental setting (about 30 minutes), the pump was started at 8 ml/min. and run for about 5 minutes until gastric contents were exhausted. The gastric juice (approximately 40 ml) was collected in the beaker and set aside. The speed was then set at 3 ml/min., and the contents placed serially in the test tubes 1-20, changing every 60 seconds. The volume of the contents of the tubes was then read from the calibrations, and the pH of the contents assayed with a Beckman combination electrode and Zeromatic I pH meter.

Acid volume and concentration were not assayed since the minute to minute variability in volume and pH appeared grossly unacceptable. The results are shown in Figure 2.1. The volumes ranged from 0.4 ml to 2.5 ml within two minutes (a factor of 6) and pH from approximately 2.0 to 4.4 (a factor of more than 200 on a linear scale) within 60 seconds. No pattern of relationship was apparent between the two measures, except that pH appeared highest in the minutes following the lowest volume. This extreme variability is possibly related to the viscosity of the gastric juice.

Regardless of the explanation, it was clear that subtle changes in gastric secretory activity would be completely masked by the variability inherent in the collection technique. Furthermore, the time required from collection of the juice to outflow from the tube was more

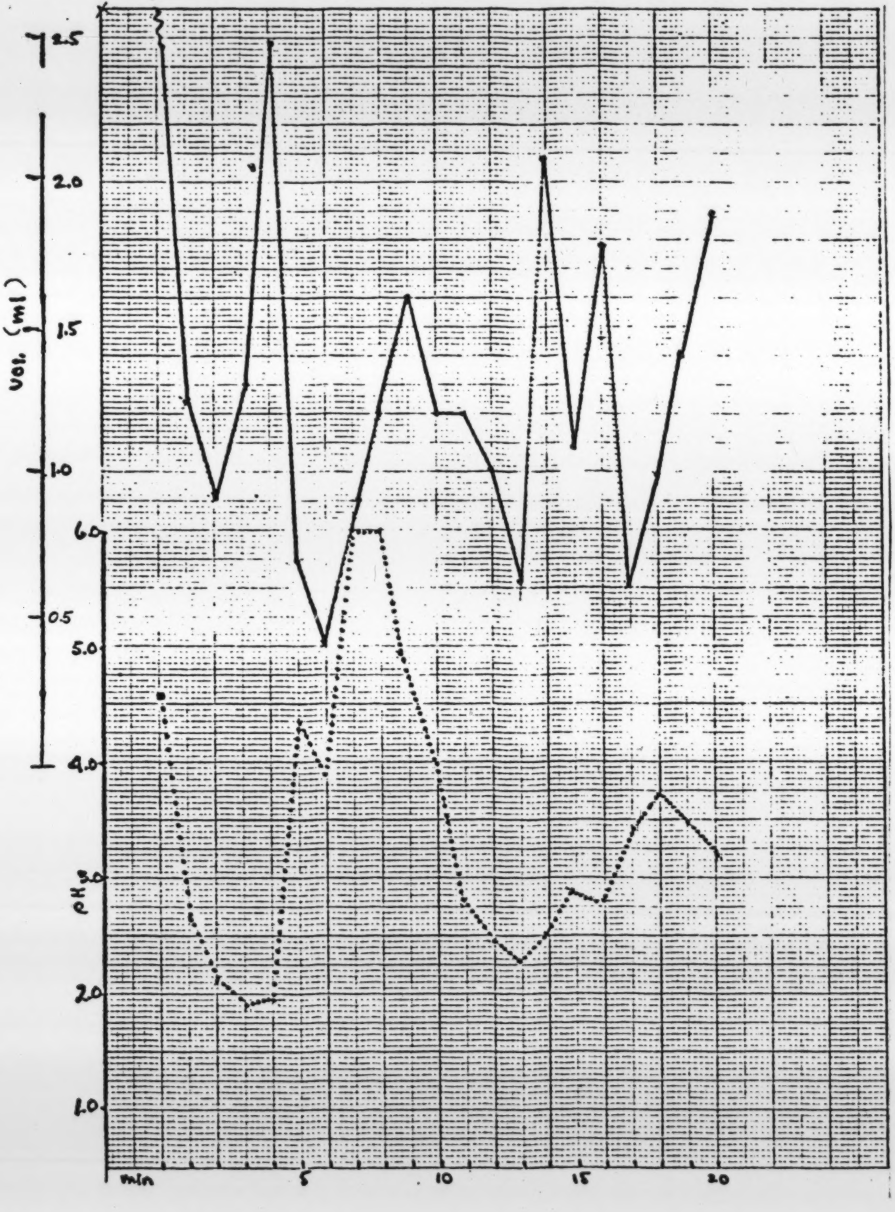

Figure 2.1 Minute by minute variation in the volume and pH of gastric samples obtained by continuous aspiration.

than five minutes, which precluded application as a feedback technique.

Welgan's solution to the delay of information incurred by the aspiration technique was to place a pH electrode in parallel with the collection tube and to give subjects continuous auditory information regarding the pH of the aspirate. Whitehead, Renault, & Goldiamond (1975) have commented on the confusing message presented to a subject by a logarithmic scale such as pH. Changes in acid secretory rate in the range from pH 2.0 to 3.0 are ten times greater than those from 3.0 to 4.0, for example. Moreover, the subject cannot determine whether the changes are due to modifications in secretion of acid or of other secretions. And changes in intragastric pH have predictable effects on other gastric processes, including acid secretion, as mentioned earlier.

While pH feedback is a confounded and inaccurate guide to acid secretion, its sensitivity and speed seem to provide enough information to direct the subject's efforts to a limited degree (Gorman & Kamiya, 1972; Welgan, 1974).

In 1973 Fordtran & Walsh reported success in observing the rate of acid secretion in response to a meal by titrating the gastric contents continuously. Their method was to aspirate a 2-3 ml sample approximately every 90 seconds, measure its pH, and introduce enough sodium bicarbonate into the stomach to bring the pH to 5.5. Once the intragastric pH of 5.5 was established, the meal was eaten. Sampling and intragastric titration continued at about 3 minute intervals, and the cumulative volume of titrant recorded. This technique had the capability of providing sensitive and accurate measurements by converting the volume of titrant per unit time to its acid equivalent. They reported a correlation of 0.92 between repeated observations of six subjects. The speed with which aspiration and pH assessment could be done, and the desired pH established intragastrically are not reported.

Whitehead et al. (1975) used a somewhat similar technique. They also infused titrant into the stomach directly, but used an intragastric electrode to assay pH. Rather than establish a stable pH, they brought the intragastric pH up to 7.0, allowed it to return to 2.0, and then neutralized it again. The amount of titrant required was converted to milliequivalents, and divided by the time elapsed to give a rate of acid secretion over time. When this method was compared with aspiration under basal and stimulated conditions, generally higher rates of secretion were noted by intragastric titration, and somewhat better reliability for aspiration. The feedback was directly related to pH changes rather than secretory rate. While speed was achieved by this approach, it seemed to involve the very complications mentioned by these authors earlier, namely that the logarithmic scale of pH changes is not immediately meaningful to most subjects.

The sensitivity and accuracy of this technique were apparently adversely affected by the manner of its application. The titration curve for hydrocholric acid against sodium bicarbonate in a closed system varies with end points above pH 5.5 due to the CO_2 present (Fordtran & Walsh, 1973). The repeated manipulation of pH from 2 to 7 would trigger reflexes at the gastric and intestinal level which would affect acid secretion in turn.

The information provided by this sort of technique would mean more to a subject if it were a linear representation of acid secretory rate, and variations represented chiefly the deliberate efforts to control cephalic signals. Clearly a modification of this technique would

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be required to do this.

The Continuous Intragastric Titration Technique

If the intragastric pH could be maintained at some steady state, the amount of titrant required to maintain that state would be a linear equivalent of the volume of acid being secreted, and any time division would give a rate proportional to the secretory rate. If adequate mixing were promoted, sensitive, accurate feedback of the secretory rate could be presented with the necessary speed.

An apparatus for maintaining a constant pH in a changing medium exists. Radiometer manufactures a pH meter which can be coupled to a burette which automatically dispenses the titrant necessary to achieve a selected pH end point. When titrating an acid with a base, for example, if the pH is below a certain end point, a relay opens causing the burette to discharge titrant into the solution. As the pH approaches the end point, the rate of discharge decreases to avoid overshoot, and when the end point is reached, the discharge is inhibited. If the pH of a changing medium drops below the determined set point, the process repeats. Used in this way, the assembly is called a "pH-stat."

The sensitivity and accuracy of this assembly depends on several factors: among these are the pH electrode, the pH meter, the concentration of the titrant, and the quantification of the titrant discharge. When properly standardized the Beckman intragastric electrode (model 39042) employed was guaranteed accurate within ± 0.02 pH. With rapidly changing pH in the solutions measured, the error was somewhat greater. In the working pH range, this error is well within the requirements of the system. The pH meter (Radiometer model TTT11) is extremely accurate

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and reliable.* The automatic burette (Radiometer model ABU 1a) measures the titrant to 0.00 ml.* With 0.1N titrant, the resolution well exceeded the requirements for accuracy stated above.

The selection of a suitable pH end point was based on several considerations: normal intragastric pH levels, optimal performance range of the apparatus, and pH regulated gastric reflexes. Between meals, human intragastric pH ranges from approximately 1.5 to 3.5 (Wolf, 1965). The titration curve for hydrochloric acid with sodium bicarbonate allows very sensitive and accurate assay of unbuffered acid at an end point of 3.5 (Kristensen, 1975). By disregarding the neglible amount of acid which is unbuffered, intragastric contents can be assayed within the physiological range. The electrodes and meter are standarized easily, and function quite well in such a medium. Gastrin response to vagal stimulation is uninhibited by pH sensitive gastric reflexes at this pH (Anderson & Olbe, 1964) and gastric emptying is slowed (Davenport, 1971). These considerations led to the decision to use pH 3.5 as an end point. Stabilizing this end point required adequate mixing of gastric contents. Fordtran & Walsh (1973) commented on this problem of adequate mixing in their technique. Grossman & Knoturek (1974) reported good success with intragastric titration of the fistulated dog stomach by continuously flushing 25 ml of fluid back and forth 7 times per minute with a large syringe. While this seemed impractical in the intact human, a workable substitute was found by loading the stomach with 200 ml of water at the start, and continuously infusing water at 10 ml/min. with a peristaltic pump (Sigmamotor model T56). By monitoring

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*The performance of this equipment exceeded our facilities for assessment.

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gastric contents with two electrodes 10 cm apart, it was determined that adequate mixing was thus insured, and that electrode placement was not as critical as it might have been otherwise (Figure 2.2). Preparations were made for the likely event that subjects would need to urinate: a urinal for male subjects and a chamber pot for female was placed in easy access to the subject.

After trying several strengths of titrant (1.0N, 0.6N, 0.3N), a solution of 0.1N seemed to work most satisfactorily. It mixes well and gives good resolution in titration.

The speed of response of the system was tested by titrating 2 ml 0.1N HCl in a 12 ml test tube gently shaken by hand. When the pH was brought to 3.5, the addition of a drop of HCl lowered the pH within five seconds, causing a response by the assembly which returned the pH to set point within 30 seconds.

An important decision for the outcome of the research was the speed at which the autoburette discharged. Pilot work showed that a successful stimulus could cause an increase in acid secretory rate of several hundred percent, so that no speed would be practical for all conditions. By adopting a rather dilute titrant, danger of overshooting was minimized, and the problem became principally that of keeping up with secretory rate. A decision rule was formulated that if the pH fell a full point below the set point and remained there for more than two minutes, the speed would be doubled. If overshooting did occur (exceeding the end point by 1 pH point for two minutes) the speed would be reduced by half. In practice, overshooting was rare.

In addition to the cumulative titration record made by the titrograph, a polygraph record of the pH excursions was maintained at

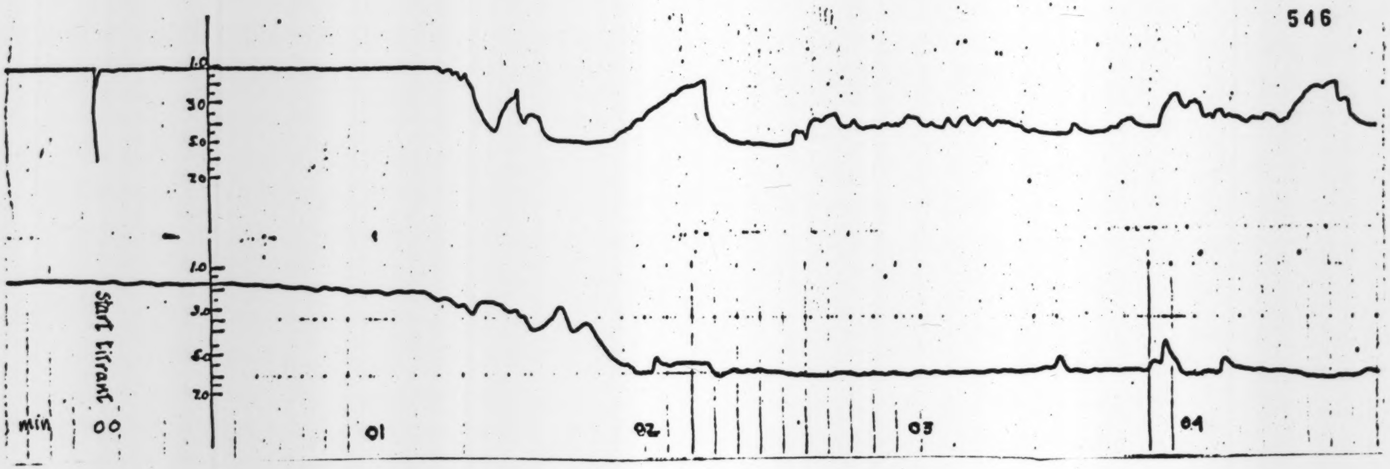

Figure 2.2 Simultaneous recording from two intragastric pH electrodes 10 cm apart. Vertical lines mark time at 1 mm/sec. Horizontal lines indicate pH, with calibrations at the left. Titrant flow began at minute 0. The distal electrode (upper tracing) in connected to the pH stat.

such a gain that 1 cm represented approximately 1 pH point. (Settings were: time constant: DC; High Frequency Filter: 3; Preamp.: 2V/cm; Power Amp.: X 1.) This produced a clear cumulative record so that these decisions could be made rapidly and objectively. A sample of this recording is shown in Figure 2.3.

The active intragastric electrode is sensitive to the hydrogen ion surrounding it and requires a reference electrode to determine the resting potential of the environment for comparison. A salt bridge was prepared by filling a six foot length of PE 260 tubing with 5% KCl suspended in 4% agar jell. One end was taped 1 cm from the glass bulb of the active electrode, and the other immersed in a jar of 5% KCl in water along with a Beckman electrode. The bridge was replaced at five day intervals, or sooner if it seemed to be causing artifact.

To assure comparability of results throughout the experiments, the titrant was carefully prepared in a ratio of $8.401 g NaCHO_3/l H_2O$ and titrated frequently against a standard solution of 0.1N Hcl (Appendix A). When not in use, solutions were refrigerated. The salt bridge was also refrigerated between experiments.

The apparatus introduced orally into the subjects consisted of a bundle of three tubes and a cable tightly wrapped with $\frac{1}{2}$ inch bands of Blenderm tape, so that the diameter was roughly 7 mm. The tubes were all polyethylene 260. The arrangement placed the reference bridge 1 cm from the electrode bulb, the titrant 5 cm from the bulb, and the water 10 cm. Each tube was cut tapered as shown in Figure 2.4 and wrapped just adjacent to the opening to minimize the discomfort of swallowing. The rationale for this arrangement is this: the reference potential immediately adjacent to the active electrode is the best comparison, but

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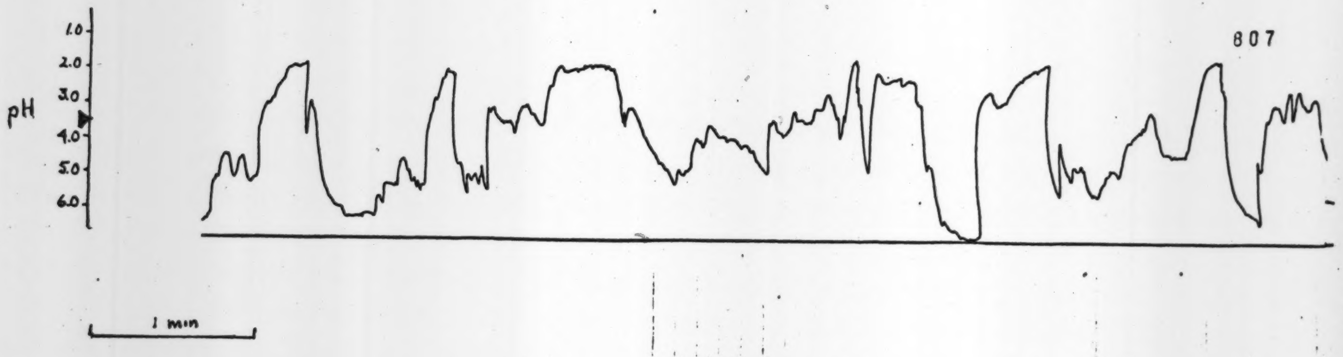

Figure 2.3 Sample pH recording from one intragastric electrode at the standard settings for the series of experiments. Vertical lines mark time at 1mm/sec. Horizontal lines on curvilinear grid mark pH as calibrated.

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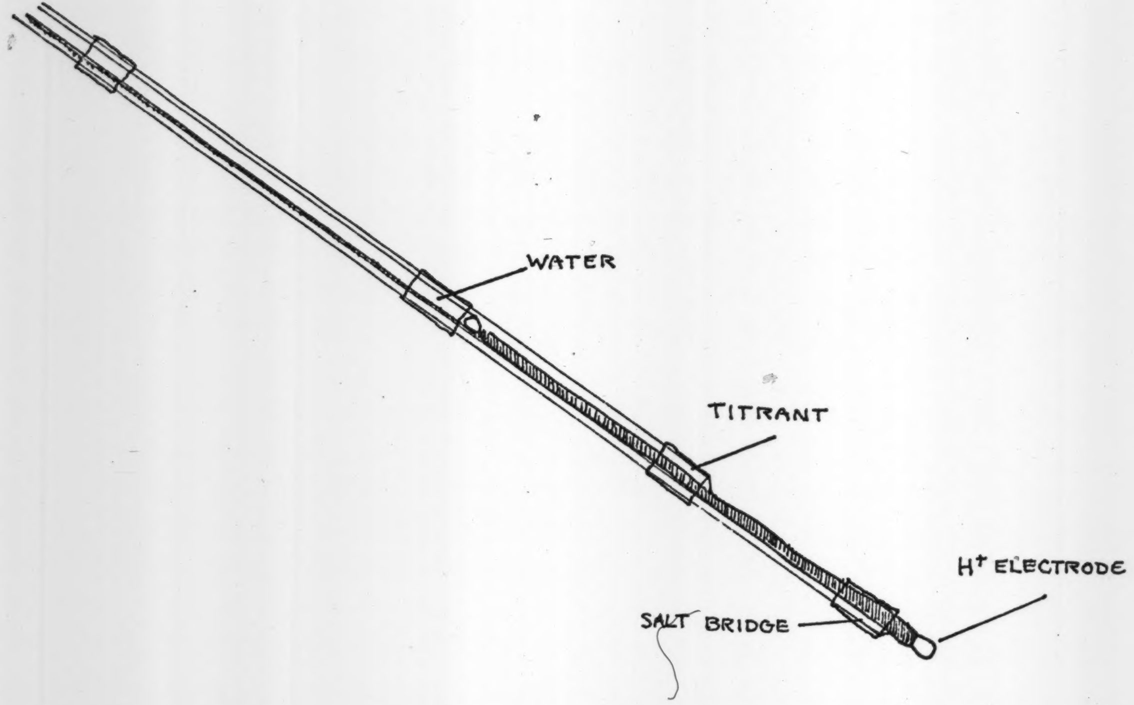

Figure 2.4 Intragastric apparatus, showing relative position of the electrode, salt bridge, and outlets for titrant and water, and the approximate diameter of the bundle

the titrant outlet must be somewhat removed from the active electrode so that it will mix with the surrounding juices before it reaches that electrode. This mixing will be promoted if the steady stream of water flows from above, trickling down the bundle past the titrant outlet. All these events take place in an area smaller than the entire stomach, because the rugae in the stomach lining prevent complete and rapid mixing.

To protect the tubing, a heavier piece of polyethylene about 3 cm long with an internal diameter of 0.9 cm was taped around the bundle where the incisors are located. The position of this protector was determined by observing the distance from incisor teeth to cardiac opening for each subject, as it can be observed in the abrupt pH shift when the electrode assembly is withdrawn. To place the electrode in the corpus or antral region, the apparatus was passed 15 cm beyond the cardiac opening.

After each experiment the bundle was disassembled, scrubbed, and air-dried. The tubes for titrant and water were scrubbed and inspected, hung to dry, and re-used on the same subject. The reference bridge was scrubbed exteriorly, the ends cut back one inch, and stored in a refrigerator at about -5° C.

The electrodes were checked every 3-4 weeks, and any time one seemed to malfunction. Two electrodes were used throughout the experiment, and both proved stable and reliable.

Effect of the Continuous Intragastric Titration Technique on Gastric Secretion

The method of observation must be unobtrusive so the observed process is not obscured. Feurle (1975) has reported that serum gastrin was notably increased when intragastric pH was elevated by continuous infusion of antacids in ulcer patients and normals. Hansky, Korman, & Cowley (1971) also noted an increase in circulating gastrin during infusion of sodium bicarbonate in duodenal ulcer patients. Neither elevated pH nor the antacid is considered the cause of the elevated gastrin levels, but rather the condition under which other stimuli provoke release (Grossman, 1967). Distention from increased gastric volume is such a stimulus. The values for basal secretion of acid in normals would therefore probably appear somewhat higher with the intragastric titration technique than with aspiration. If the rate is constant, however, and the variability slight, changes in acid secretory rate due to cephalic influences would be noticeable.

To determine what rate of basal secretion would occur and the degree of variability from moment to moment independent of experimental stimulation, three normal subjects were recruited for observation. Two males and one female between the ages of 24 and 27 with no history of internal disorder responded to advertisement. None were taking any medication or regularly using drugs.

Apparatus. The pH stat assembly described above was connected to a recording titrograph (radiometer model SBR2C) which plots cumulative titration over time. An assistant recorded the readings of the volume register on the autoburette every 15 seconds as well. The pH stat, recording assembly, water pump, and polygraph were in a room adjacent to the subject room and the cables and tubes passed through a small port in the wall. A lounge chair was positioned next to this port with the backrest at approximately 65° from horizontal.

Procedure. The subjects were habituated to the experimental setting and procedure by 6-14 sessions of observation. Each understood he was to fast from dinner the previous night, except for water upon arising, and arrive between 8 and 9 a.m.

On the days of data collection, the subject would first be asked to use the bathroom to urinate. He would then be seated in the experimental chamber and given a 200 ml beaker of water at room temperature. He was told to sip this if he liked as he swallowed the electrode bundle, and to drink it all once the electrode was in place.

The pH meter was standardized daily with pH 4 buffer before the subject's arrival, and the polygraph was calibrated. While the subject was swallowing the water, the pH changes could be observed as a check for proper functioning. When the apparatus checked out properly, the water pump and titration assembly would be started, and titrant volume recorded every 15 seconds according to a stop watch attached to a clipboard.

The subjects were permitted to read light literature--science fiction or the daily paper--during the first 30 minutes while the end point was being established in the stomach and during the 60 minutes recording. At the end of the recording session, subjects were offered a light breakfast and paid $4 an hour for their participation.

Results. The results of the baseline recordings showed an average rate of 12.3 mEq/hr. or 0.205 mEq/min. Variability was calculated in terms of the standard error of the slope of cumulative titrant, and average 0.043 mEq. The results of the individual baseline sessions are presented in Figure 2.5. The figures are drawn from the cumulative titrant readings at 5 minute intervals. The first 20 minutes are not useful descriptions of gastric secretory activity, since the

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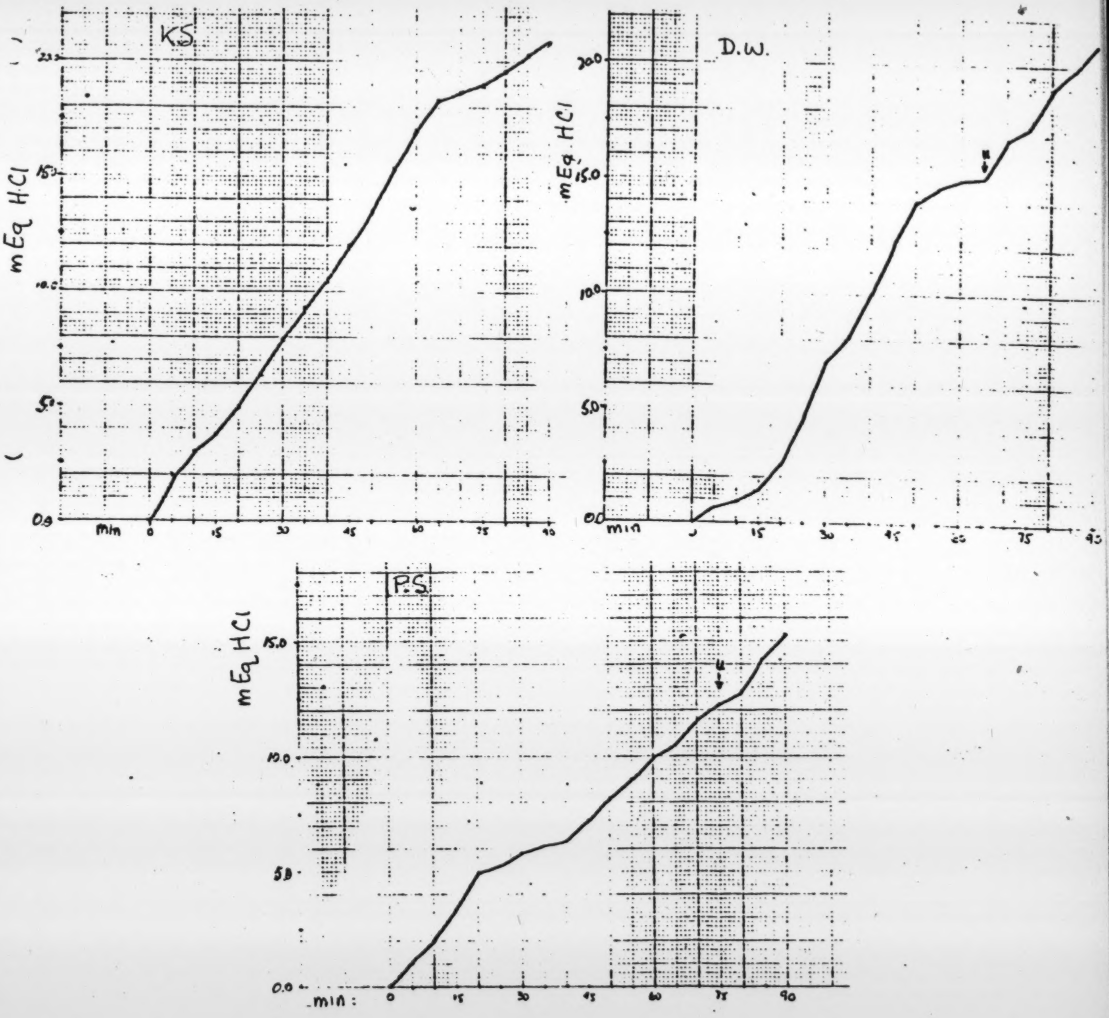

Figure 2.5 Baseline cumulative titration curves for subjects K.S., D.W., and P.S. Values of the ordinate are milliequivalents of hydrochloric acid. Time is in minutes. Data points are cumulative volumes over 5 minute intervals. Time of urinating (u) indicated by arrows.

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end point was being established during that time. The plateau observed in the P.S. record, beginning at minute 20 can be attributed to the higher rate of titration before equilibration at the end point. After that plateau, from minute 40 the rate appears to be quite stable. The plateau probably represents an overshoot.

The record for K.S. shows a more constant rate of titration and better mixing. Here again, there is a leveling off beginning at minute 65. This could possibly be due to emptying. Some 20 minutes later the subject expressed an urgent desire to urinate. By this time she had received approximately 1.250 liters of fluid over 85 minutes time.

The record for D.W. shows a leveling off from minute 50 until 65, when it resumes at a rate resembling the overall rate for the session. Again, the reason may be emptying at minute 45, since the subject announced that he was urinating at minute 65. This pattern is not always seen in connection with urinating. Subject P.S. urinated at minute 75 of the charted data, but does not exhibit any preliminary emptying or plateau. Overall, urinating affected the cumulative record, but not in a predictable manner.

These records* were fitted to polynomial curves to determine whether a linear fit was most appropriate. The results of these analyses are shown in Table 2.1. In all cases the linear was by far the principal component, as is evident from the very high correlation values (.981, .985, and .991) and the small standard error about the first degree equation.

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*The data analyzed were the cumulative values over 60 second intervals beginning with the 21st minute after titration was started.

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Table 2.1 Rates, Linear Regression and Correlation Coefficients for Basal Acid Secretion in Three Subjects

Subject	Rate		Regression coefficient		Correlation coefficient
	mEq/hr	mEq/min	B	S.E.	[cum. vol x min]
D. W.	13.92	0.232	2.387	0.057	0.981
K. S.	12.95	0.216	2.406	0.052	0.985
P. S.	9.41	0.157	1.511	0.025	0.991
X	12.28	0.205			

Basal secretory rates are known to be highly variable. Under maximal stimulation, this variability is greatly reduced. Other baseline observations are not available for comparison, but further comment on this point will be made in subsequent chapters.

Discussion. The basal rates observed are higher than those reported with aspiration techniques. Davenport (1971) states that the rate of secretion observed by aspirating and titrating in vitro to pH 3.5 was 2.4 ± 2.85* mEq/hr. for 615 men, 1.3 ± 2.0* for 634 women. Kristensen (1975) reported very similar averages (1.4 ± 1.3* mEq/hr.) for 9 men and women when she measured total acidity in vitro. Fordtran & Walsh (1973) observed basal secretion for 6 normal subjects while titrating intragastrically and reported an average of 1.4 ± 1.6* mEq/hr. Six basal recordings by Whitehead et al. (1975) average 4.8 mEq/hr.

The reason for such a large difference between my observations and these reports may be the technique itself. Feurle (1975), Hansky, Korman, Cowley, & Bacon (1971) have observed the large increases in circulating gastrin under conditions of elevated intragastric pH. Under such conditions, vagal stimulation has a heightened effectiveness (Korman, Hansky, Coupland, & Cumberland, 1973; Knutson, Bergegardh & Olbe, 1974; Hansky et al., 1971). Gastrin concentration is also known to increase at meal time (Feurle, Kelterer, Becher, & Creutzfeldt, 1972) partially due to vagally transmitted circadian rhythms. Gastric distention causes vagal excitation of acid production (Grossman, 1962) which is greatly increased by circulating gastrin (Grossman, 1961). The high rates of secretion observed in three subjects could well be due to vagal stimulation in the presence of elevated gastrin levels. Because

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*Standard deviation.

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these rates are so high, they can be considered "basal" only in comparison to the other trials reported using the same technique.

The rates of secretion recorded by intragastric titration in response to food stimulation (30 mEq/hr.) peak histamine (34.5 mEq/hr.) and submaximal histalog stimulation (17.2) for normal subjects (Fordtran & Walsh, 1973; Feurle, 1975) are higher than these figures. The technique seems to produce an intermediate rate of secretion, then, which would be useful for observing increases and especially decreases due to cephalic control.

Variability is commonly correlated with the magnitude of a variable. The size of the standard error observed is larger in this case than would be desired, since it would obscure the meaning of changes in secretory rate smaller than about 30%.

The variability may be due to underlying physiological events or to characteristics of the technique or to both. By simultaneous observation of gastric motility, electrode placement, turbulence patterns of gastric contents, general vagal tone, levels of gastrin, etc., sources of this variance might be partialled out. Whitehead et al. (1975) noticed no association between secretory rate and either motility or general vagal tone. Such measures were not undertaken in this study, unfortunately, so no alternative was apparent but to accept and work with the variability.

The intermediate rate of secretion and its associated variability must be evaluated in terms of the size of the changes to be observed. The technique developed seems to offer sensitivity, accuracy, and sufficient speed to be useful as a monitor for biofeedback, as long as the changes are great enough to be detected against a background of considerable unassigned variance, or noise. Whether prompt and meaningful feedback could be given required a knowledge of the speed and magnitude of the expected changes. The next chapter will present data relevant to that question.

Chapter 3

OBSERVATION OF THE ACID SECRETORY RESPONSE TO EXCITATORY AND INHIBITORY VISUAL-OLFACTORY STIMULI

Introduction

Researchers have been limited by their technique in the studies of the time course of cephalic influences on gastric acid secretion. Very little attention has been given to an inhibitory influence of cephalic origin, so its time course is an even greater mystery than excitation. Two studies employing the technique just described will be reported, one of excitatory cephalic activity and one of inhibitory activity. The results of these studies raise some interesting questions for the application of this same technique to instrumental conditioning of the same responses.

Review of the Literature

Pavlov (1902) observed the phenomenon of unconditioned increase in the rate of secretion of both saliva and gastric juice in dogs upon the presentation of food. Sham-feeding (diverting food away from the stomach through an esophageal opening after it has been tasted, masticated, and swallowed) excited secretion for as long as 90 minutes, and simply the sight and smell of food provoked it for 34 minutes. He also observed the prolonged inhibition of secretion due to fright in these same animals.

Miller, Bergeim, Rehfuss, & Hask (1920) reported the effect of pleasant and unpleasant alimentary stimuli on aspirated gastric secretion in intact humans. The sight of an attractively served nutritious meal provoked increased volume of gastric juice but an unattractively served one did not. Odor alone produced more secretion than sight alone, or the sound of preparation, or the thought of food. Following an increase in volume of juice due to the smell of food, a foul smell (animal waste) brought the rate back to normal. These observations are on only one to three subjects, the results inconsistent, the time relationship of stimulus presentation and the responses are unclear. Latencies appear to be on the order of 10 to 15 minutes.

Wolf & Wolff (1947) documented the responsiveness of Tom's fistulated stomach to various stimuli, showing approximately 100-200% increase above baseline acid secretion at 10 and 25 minutes respectively in response to the smell of coffee and the taste and discussion of food. Precise time relationships were confounded by the order of presentation, however.

Janowitz, Hollander, Orringer, Levy, Winkelstein, Kaufman, & Margolin (1950) studied the response of a woman with complete obstruction of the esophagus to sham-feeding by aspirating gastric contents through a stoma. Depending on the palatability of the meal tasted, acid secretion changed from -50 to +400% in 15 minutes. The latent period was determined to be three minutes in one instance. In this subject, the peak acid secretion (average 20.4 mEq/hr.) occurred most often during the third 15 minute collection (i.e., from minute 31 to 45), but was highly variable. The duration of the response also varied around a mean of 60-75 minutes.

Parker, Werther, & Hollander (1963) studied another female patient with obstructed esophagus and gastrostomy. Sham-feeding produced an average increase in acid secretion from 3.8 mEq/hr. to 6.5 mEq/hr within the first hour--a response greater than her reaction to strong histamine stimulation.

Kehoe & Ironside (1963, 1964) investigated the gastric response to hypnotically induced images of food and eating, disgust, nausea, and a variety of emotional states by aspirating normal subjects. The sight and eating of food, when induced hypnotically, provoked secretion. The lowest rates of secretion occurred in the state of hypnotic nausea. Their data must be considered in light of the fact that hypnotic induction itself reduces secretion (Hall, Herb, Brady, & Brooks, 1967; Eichhorn & Tracktir, 1955).

Preshaw & Webster (1967) observed that sham-feeding dogs provoked acid secretory responses similar to those following infusion of gastrin extract or histamine. Teasing with food caused a weaker response. Large increases (300-600%) were seen in the first 15 minutes following sham-feeding. The secretory rate peaked during the second 15 minutes and remained above basal levels for approximately two hours. When the pH sensitive region of the antrum is kept neutral by surgical exclusion of gastric juice, sham-feeding responses of 1500% (Olbe, 1963) to 2000% (Preshaw, 1970) have been observed.

In duodenal ulcer patients, sham-feeding while maintaining a neutral intragastric pH resulted in large increases in acid secretion; pentagastrin under the same conditions caused even larger ones (Knutson et al., 1974).

Excitatory Stimuli

The effect of the sight and smell of food on the intact normal human with neutralized antrum is not known. Observations done with the

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intragastric titrating technique would provide some description of the time course and magnitude of cephalic influences. Since ample circulating gastrin would likely be present, large responses could be expected. The difference between stimulated secretion and basal rate would possibly be less than observed in previous studies because of the relatively elevated baseline. Since the neural excitation of acid-secreting cells is the principal mechanism of interest (Preshaw, 1970) very brief latencies would probably characterize its action.

Method. The same three subjects whose basal secretions had been observed by intragastric titration were observed in two conditions: (a) the presentation of excitatory visual and olfactory stimuli, and (b) the presentation of inhibitory visual and olfactory stimuli. The order of presentation was randomized, but the experiments will be reported in sequence.

Each subject selected a simple breakfast menu. One subject requested a warm buttered pastry and sweetened coffee, another chose a whole wheat muffin with cottage cheese and honey and black coffee, and the third chose hot buttered muffins with marmalade and a cup of orange juice. These meals were prepared in a ventilated room remote from the subject, and were served on a bed tray which could be placed on the subject's lap. A dome covered the dish of food until presentation of the stimulus. A fresh doily, napkin, and appropriate tableware were neatly arranged on the tray.

The procedure described for baseline recordings was also followed in these studies. After 20 minutes of habituation and 10 minutes prestimulus baseline recording, the stimulus was presented. The subject did not know that on this session any stimulus, excitatory or inhibitory, was to be presented. As the experimenter entered the room, the subject was asked to stop reading, the tray put in place, and the dome lifted. Immediately 0.5 ml of the selected beverage was infused into the subject's mouth, with the instruction not to swallow but to hold the sample in the mouth and taste it. The presentation of the stimulus took approximately 10 seconds, and stimulus onset was reckoned from the moment the beverage was introduced. The tray remained in place for five minutes while the subject handled and smelled the food and beverage, and was then removed. Responses were recorded for 60 minutes following the stimulus.

To reduce the intrinsic variability of the cumulative data, a smoothing procedure was introduced which adjusted each 15 second data point as a weighted average including the three data points preceding and following it (Appendix B). The rate of change was computed from the smoothed data and plotted in 15 second intervals.

Results. The response to the excitatory stimulus appeared in two phases. The first had an average latency of 2.2 minutes, peaked at 8.8 minutes, and lasted for 16.1 minutes. The peak 10 minute rate averaged 0.223 mEq/min., a 270% increase above prestimulus rates (0.083 mEq/min. average). A second phase occurred at 18 minutes after stimulation, peaked at 23 minutes, and continued beyond the period of observation in two cases. The second peak 10 minute increase was about 290% above prestimulus levels, averaging 0.240 mEq/min.

Figure 3.1 shows the cumulative curve and first derivative (rate) for each subject. The time characteristics and percent differences for each subject appear in Table 3.1.

For biofeedback application, it is useful to examine more closely the briefest individual response latency observed. The titrograph

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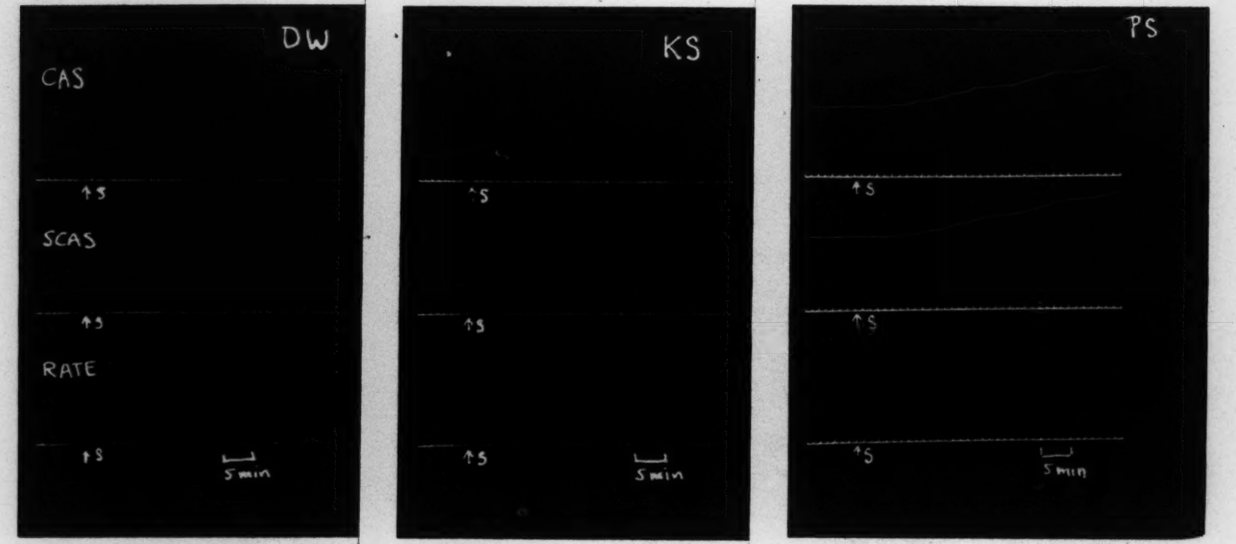

Figure 3.1 Cumulative acid secretion (CAS) before and after smoothing (SCAS) and first derivative (RATE) of smoothed data showing the response of three subjects to the presentation of an appetable stimulus (s).

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Table 3.1 Characteristics of Gastric Acid Secretory Response of Three Subjects to Excitatory Visual-Olfactory Stimuli

Subject	Baseline	First phase				Second phase			
	10 minute pre-stimulus rate mEq/min	5-15 minute post-stimulus rate mEq/min	Time characteristics (minutes after stimulus)			20-30 minute post-stimulus rate mEq/min	Time characteristics (minutes after stimulus)		
			latency	peak	duration		latency	peak	duration
D. W.	.14	.20	0.5	5.0	12.0	.30	14.5	28.0	60.+
K. S.	.10	.35	0.5	8.0	14.0	.32	14.0	18.5	60.+
P. S.	.01	.12	5.5	15.3	22.5	.10	26.0	32.8	38
X	.08	.22	2.2	8.8	16.0	.24	18.1	26.4	

recording appears in Figure 3.2. The latency appears to be extremely short, less than one minute.

Discussion. The excitation of secretory activity by food teasing while maintaining neutral intragastric pH and moderately high rate of secretion produces strong responses.

While the average latency of the initial response is in close accord with that observed by Janowitz et al. (1950), it is possible that the true latency is briefer. The briefest latency was not out of character with preliminary observations during pilot studies when such brief latencies were seen several times. Carlson (1920) remarked that vagal stimulation during high rates of secretion provoked increases with almost no noticeable latency. Because of the delay in recording response inherent in this technique it is not possible to exclude the possibility of latencies shorter than 60 seconds.

A vexing problem in locating the precise point at which the secretory response occurs is the frequent appearance of an anticipatory response one to three minutes before the stimulus onset. Despite efforts to control them, it seems there were sounds perceived by the subject as preparations for stimulation. Since the anticipatory response was consistently one of increased acid secretion, and it was seen prior to both types of stimulus, smell was probably not a significant factor. Subjects seem to become classically conditioned to feeding cues very quickly, and to have very low thresholds for physiological response to those cues.

The bi-phasic character of the response may be due to underlying physiological mechanisms, neural and hormonal, respectively. It may also be an effect of the titrating technqiue: when the rate of secretion initially increases, the speed of titrant flow is also increased until

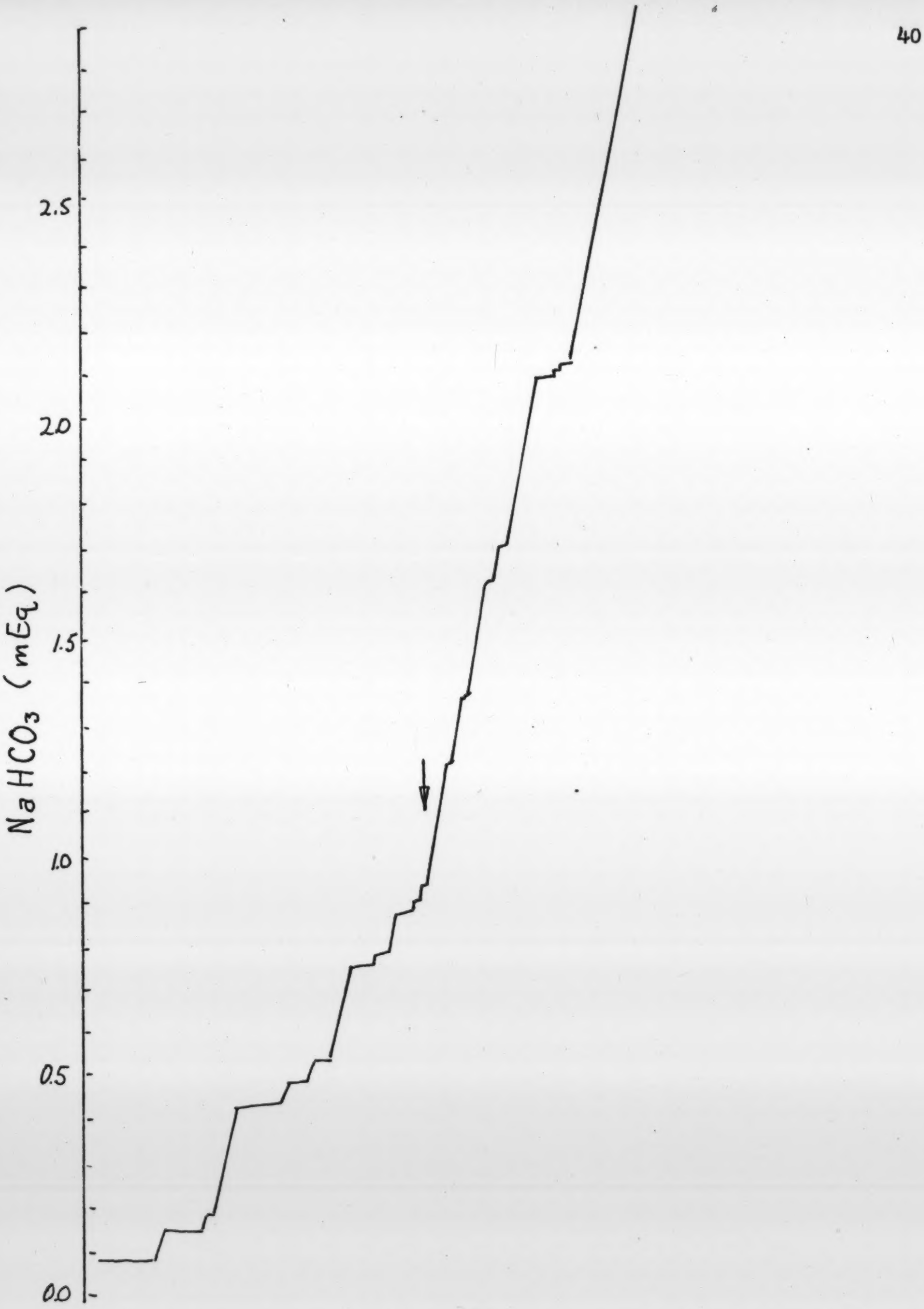

Figure 3.2 Response of subject K.S. to excitatory stimulus traced from titrograph record.

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a stable state or overshoot occurs. In one of the three cases, however, the initial phase was rather weak, and a strong response did not appear until 14.5 minutes after stimulation, a sequence of events which could not be explained as an artifact of the technique.

The second phase appears both stronger and longer-lasting than the first. Also, it seems invariably to follow, even when the first is quite weak. The implications for biofeedback application are problematic: if cephalic excitation produces a chain of responses, the first of which may be quite subtle, the key information for feedback is the initial activity which might precipitate a prolonged and amplified reaction.

Inhibitory Stimuli

Miller et al. (1920) reported a transitory partial inhibition of acid secretion due to a foul smelling stimulus. Quantification of the acid secretory decrease is not available. Kehoe & Ironside (1963, 1964) noted a prompt decrease in secretory rate in their hypnotized subjects when disgusting or nauseating experiences were induced. There are no reports of the transitory inhibitory action of cephalic control under conditions of neutral antral pH.

To describe that response, a strong negative stimulus (canine feces) was selected for presentation to the same subjects. The context of stimulus presentation was directed to alimentary response centers by arranging this stimulus in the same manner as the food, to enhance its disgusting and nauseating quality. Because the nature of the stimulus was ambiguous until the moment of showing it to the subject, precise stimulus onset could be determined.

A fairly prompt and transitory reduction in secretory rate was expected to result from exposure to an offensive visual-olfactory stimulus. Wormsley (1970) has recently commented on the frequent occurrence of a rebound following inhibition. The period of observation allowed time to see such a later phase.

Basically the same subjects and procedures described above were employed. Fresh canine feces were obtained for each presentation. To increase olfactory impact, they were placed on a dish, covered with the dome, and warmed for 15-20 minutes beforehand. After 30 minutes of baseline recording, the stimulus was presented on the tray, and left in place five minutes. The room was ventilated after removal of the stimulus, and responses were recorded for 60 minutes.

Results. One subject, though visibly disgusted by the stimulus, did not show any secretory inhibition at all. The two other subjects, however, exhibited remarkably similar responses. After a 30-45 second latency, their combined secretory rates reduced by exactly 50%. The nadir rate occured at 4-8 minutes after onset of the stimulus, and duration of the first phase was from 8 to 18 minutes. After 18.5 minutes, both subjects exhibited a rebound of approximately nine minutes duration, reaching 100% increase above prestimulus levels in one subject.

The cumulative curves and rates for all subjects appear in Figure 3.3, the time and amplitude characteristics in Table 3.2.

Discussion. When acid secretory rate is fairly high and gastric pH maintained neutral, an offensive sight and smell can cause a significant transitory inhibition. During pilot observations the same complex occurred once in subject P.S. and three times in subject D.W. The third subject, K.S., never exhibited an inhibitory gastric response to stimulation, even though her outward response of disgust was the most pronounced of all subjects, her response to excitatory stimuli was quite

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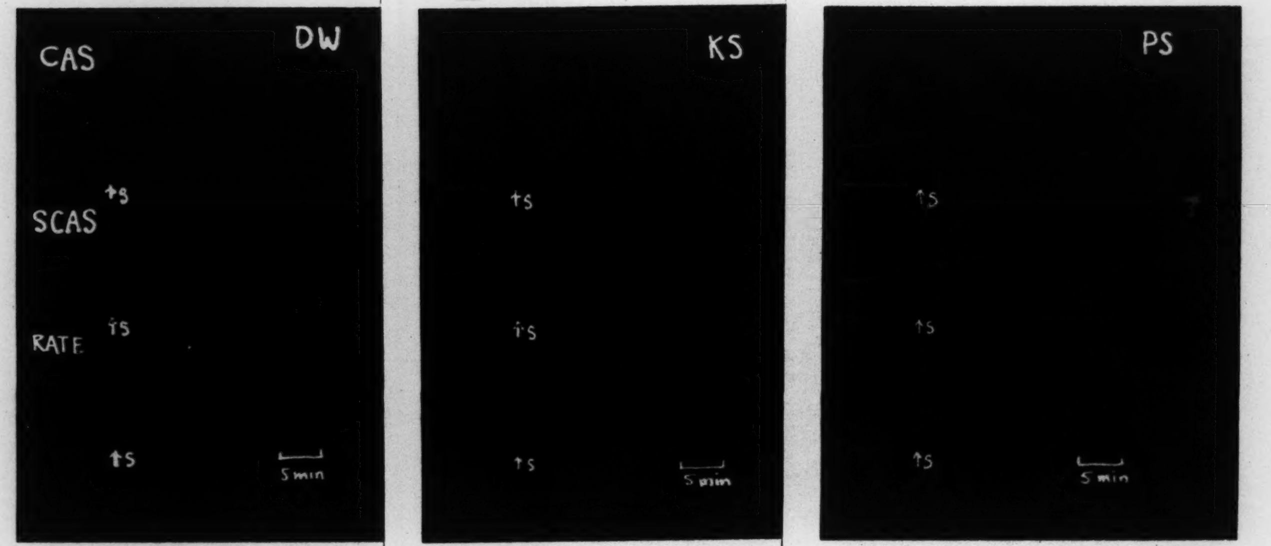

Figure 3.3 Cumulative acid secretion (CAS) before and after smoothing (SCAS) and first derivative (RATE) of the smoothed data showing the response of three subjects to the presentation of a disgusting stimulus.

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Table 3.2 Characteristics of Gastric Acid Secretory Response of Three Subjects to Inhibitory Visual-Olfactory Stimuli

	Baseline	First phase				Second phase			
	10 minute pre-stimulus rate	5-15 minute post-stimulus rate	Time characteristics (minutes after stimulus)			20-30 minute post-stimulus rate	Time characteristics (minutes after stimulus)		
Subject	mEq/min	mEq/min	latency	nadir	duration	mEq/min	latency	peak	duration
D. W.	.45	.21	0.5	8.5	18.0	.49	19.0	23.5	28.0
K. S.	.30	.31				.24			
P. S.	.25	.14	0.8	4.0	8.0	.37	18.5	22.0	27.0
X (D. W. + P. S.)	.35	.17	0.7	6.3	13.0	.43	18.7	22.7	27.5

strong, and her success in the voluntary inhibition of acid will be seen to have been outstanding.

The explanation for diminished or absent inhibitory response may lay in the individual's conditioning history. It was apparent that repeated exposure of another subject to inhibitory stimuli produced slower and weaker responses, due probably to habituation (Figure 3.4). And subject K.S.'s null response may actually have represented the sum of an anticipatory response and a small but appropriate response to the stimulus.

The significance of the second phase rebound is unclear. On a phenomenological level, the two phases occur as though the rate of production remained constant, but release was temporarily blocked in one phase creating a backlog which combined with the normal release in the second phase. The net effect over 30 minutes was a very slight increase in rate of secretion over the prestimulus rate. Wormsley (1970) states, "The biphasic 'inhibition-rebound' type of response, for example, could be due to temporary depression with subsequent facilitation of the response to the secretory stimulant, or alternatively to two phases comprising separate and successive processes of 'inhibition' and 'stimulation' [p. 884]." Much more detailed study is necessary to corroborate the pattern observed and determine its significance physiologically.

Another explanation might be considered: that the responses observed are not entirely related to the nature of the experimental stimulus; that the experimenters' intrusion upon the solitude and monotony of the subject's chamber might provoke a characteristic response, both anticipatory and in the "second phase." If this were the case, the return of the experimenter five minutes later to remove the stimulus

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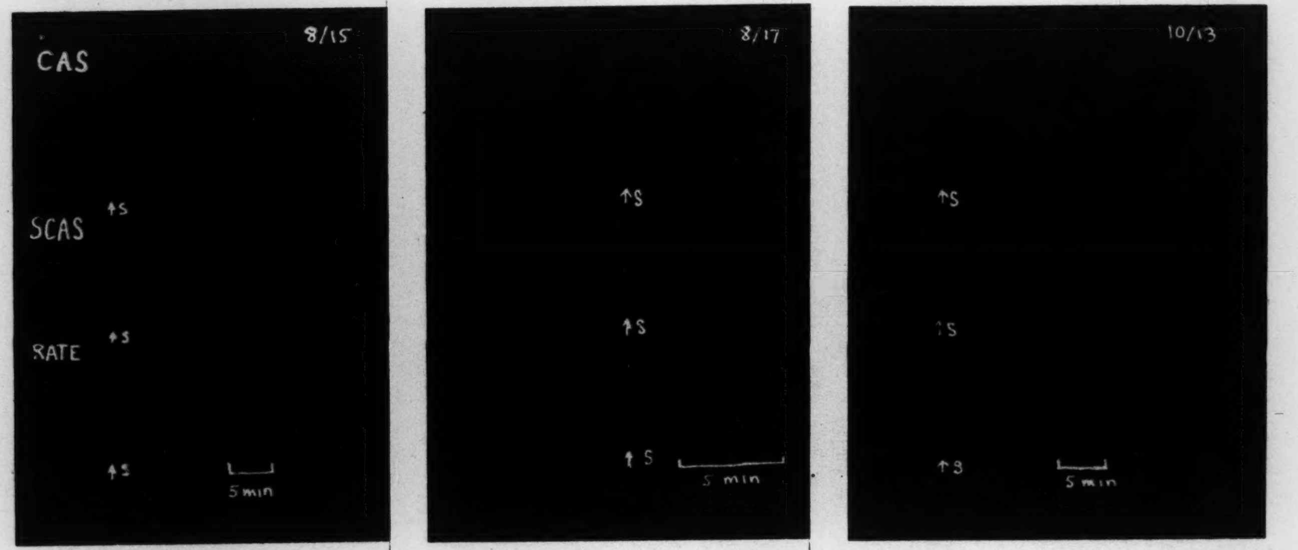

Figure 3.4 Cumulative acid secretion (CAS) before and after smoothing (SCAS) and first derivative (RATE) of SCAS showing D.W.'s response to an inhibitory stimulus (s) on three successive days.

might be expected to have a similar effect. Apparently it does not. Still this explanation cannot be ruled out.

For the purposes of this series of experiments, the data suggest certain conclusions for biofeedback application. In both excitation and inhibition, the latency of the response might be a minute or less, and the "rise time" from latency to the peak or nadir of the first phase approximately five minutes or longer. The delay between the actual change in secretory rate and informing the subject must be no greater than a minute. The assessment of the magnitude of change might encompass response patterns over periods of approximately five minutes. Assessments over much longer periods could completely overlook an effective inhibitory response.

Assuming that the same mechanisms and basic response patterns could be in effect during operant conditioning of cephalic level regulatory behaviors, efforts to increase acid secretory rate would be facilitated by second-phase events, and efforts to inhibit secretion would be countered. If a social-interaction phenomenon accounts for the second phase, these efforts would be free from such interference.

When the prestimulus rates for all subjects in all conditions are compared, there is considerable variability from subject to subject and day to day even in the same subject, as has previously been observed, and less variability from hour to hour for the same subject (Sun & Shay, 1955; Hirschowitz, Streeten, London, & Pollard, 1957). The most reasonable comparison for any change in secretion would then seem to be among rates on the same day.

Individual secretory rates on the day of the excitatory stimulus happened to be lower than for the comparable period on the day of the

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inhibitory stimulus. On the days when basal rates were recorded (Chapter 2) comparable rates were midway between these later observations. Consequently comparisons of absolute rates after the stimulus would give misleading results.

Summary

In summary, the patterns of acid secretory response to excitatory and inhibitory cephalic influences appear to have a very short latency (probably < 60 seconds) in the initial phase. A second phase follows, which may not be directly cephalic. After the excitatory response, a rather prolonged increase in rate occurs at least as large as the initial increase; following inhibition an increase also occurs, briefer and less pronounced than the second phase of excitation. Day to day fluctuations in baseline, even in a state of moderate continuous experimental excitation, exceed the magnitude of these transitory influences in an individual.

Chapter 4

OBSERVATIONS OF THE EFFECTS OF INFORMATION FEEDBACK AND REINFORCEMENT ON THE ACID SECRETORY RESPONSE SYSTEM

Introduction

A review of the recent literature suggests that normal subjects may be able to modify gastric acid secretory rate when guided by biofeedback and appropriate reward. A study will be described which sought to determine whether rapid learning of acid secretory control could be achieved, and what this might reveal about the characteristics of cephalic influences on acid secretion.

Review of the Literature

Several investigators have explored the question of whether gastric acid secretion can be modified by information feedback and reinforcement. In one of these studies continuous information regarding intragastric pH was given to the subject while rewarding him for increasing or decreasing acidity (Gorman & Kamiya, 1972). After three 60 minute trials, group averages for the nine subjects showed significant modification in the appropriate direction, both increases and decreases, with reversals in the same trial. Since pH was the only measure observed, interpretation of the phenomenon was very limited.

At about the same time Welgan (1975) was teaching ulcer patients to reduce acid secretion. His technique was described earlier. These subjects were presumably motivated by their pathologies to reduce acid

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secretion. On the whole, his subjects were able to show significant decreases in volume of secretion, acidity, and acid volume when given feedback. It is not clear how long the training period for each subject was, but it may have been only 30 minutes.

Whitehead et al. (1975) gave prolonged training with a method previously described to four subjects, three of whom demonstrated significant increases in gastric acid secretion in response to instrumental conditioning. This study was also first reported in 1972.

Moore & Schenkenberg (1973) described a single subject who apparently could increase or decrease acid secretion on command, given feedback about every 12 minutes. The protocol was particularly susceptible to experimenter bias, however, and the results must be regarded as suggestive rather than conclusive.

All of these investigators expressed reservations about the suitability of their technique or the magnitude of their results, or both. In fact, all of the techniques meet the requirements of a biofeedback technique only partially, and suggest that a better technique might yield more satisfactory results.

It seems likely that subjects can learn to modify the rate of gastric secretion, given suitable feedback and reward. Specifically, the hypothesis of this study is that normal subjects given continuous feedback of the rate of acid secretion and periodic quantification of performance can decrease or increase that rate to obtain reward.

Method

Each of the three subjects employed in previous studies received four 45 minute periods of training. Each was first rewarded for decreasing the rate of acid secretion. According to the procedural plan, if he succeeded in inhibiting acid secretion completely for 15 minutes, the next session would require increasing acid secretion to a criterion of 100%.

The technique and apparatus have been described above. For the instrumental learning sessions the pH meter was moved into the subject room and placed near the subject's left knee. The meter face, with the pH 3.5 end point marked clearly, was in easy view of the subject. A white light on the control panel flashed when titrant was being pumped, i.e., when the pH was below the end point.

The frequency of the flashes of light is inversely proportional to the natural logarithm of the difference between the pH of the medium and the end point, and therefore is directly and linearly proportional to the rate of gastric secretion, so that it provides analog feedback of that secretory rate. How much change each flash represents could be determined by the speed settings on the autoburette in the control room, allowing the experimenter to "shape" the secretory response, encouraging small changes at first, then larger and larger ones. The light and meter face were covered except during feedback intervals.

As in the other studies, subjects fasted overnight and arrived between 8 and 9 a.m. The protocol and reward contingencies were explained each day. The sessions began with 20 minutes for equilibration and 10 minutes baseline, then there were three 15 minute trials with feedback and reward, each followed by five minutes of rest. For decreasing acid secretion, subjects were told to try to keep the pH above the end point, and prevent the light from flashing. For increases, they were to try to keep the light on as much of the trial time as possible. During the rest, the difference between the day's baseline and the trial was cal-

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culated and the reward announced.

The subject was asked to make notes on a steno pad describing his strategies, state of mind, experience, etc., during the baseline and each rest period.

The reward was money, calculated at one cent for each percent difference from baseline in the proper direction over a 15 minute trial. This was quickly calculated and announced at the end of each trial, providing knowledge of results as well as reward. In addition, a $5 incentive was offered for any trial in which a 100% difference was achieved. Successful performance was also encouraged verbally via the intercom. Rewards were paid daily in cash.

Results

When the rate of secretion for each trial is compared to the basal rate for that subject on the same day, 18 of 30 attempts to inhibit acid appear to have been successful (Table 4.1). When the rates are averaged trial by trial for all days, there seems to be an effect of training on each day, with the rate of secretion progressively lower from baseline through Trial 3. This progression does not seem to carry over from one day to the next. The percent decreases from daily baseline for all trials are plotted for each subject (Figure 4.1). The degree of control on the final day of inhibition training varied, depending on how long a period was observed. Seven out of nine trials were successful compared to daily baselines. The most notable cases were a 15 minute trial in which the rate slightly exceeded baseline, followed by complete inhibition for more than 20 minutes. Each trial was arbitrarily divided into five 3 minute frames and regression coefficients calculated for each frame. When the unsuccessful trials were

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Table 4.1 Gastric Acid Secretion Rates and Percent Changes from Daily Baseline for Three Subjects Rewarded for Decreases

		Baseline	Trial 1		Trial 2		Trial 3	
Subject	Day	mEq/min	mEq/min	% change	mEq/min	% change	mEq/min	% change
D. W.	1	.167	.180	+07	.260	+55	.274	+63
	2	.233	.286	+22	.234	00	.226	-03
	3	.133	.154	+16	.286	+112	.133	00
	4	.233	.174	-24	.180	-23	.274	+17
K. S.	1	.100	.074	-26	.094	-06	.060	-40
	2	.100	.074	-26	.114	+14	.000	-100
P. S.	1	.300	.240	-20	.086	-71	.100	-67
	2	.456	.366	-20	.280	-38	.446	-02
	3	.100	.133	+33	.094	-06	.100	00
	4	.556	.446	-20	.360	-36	.280	-50
X		.238	.213		.199		.189	

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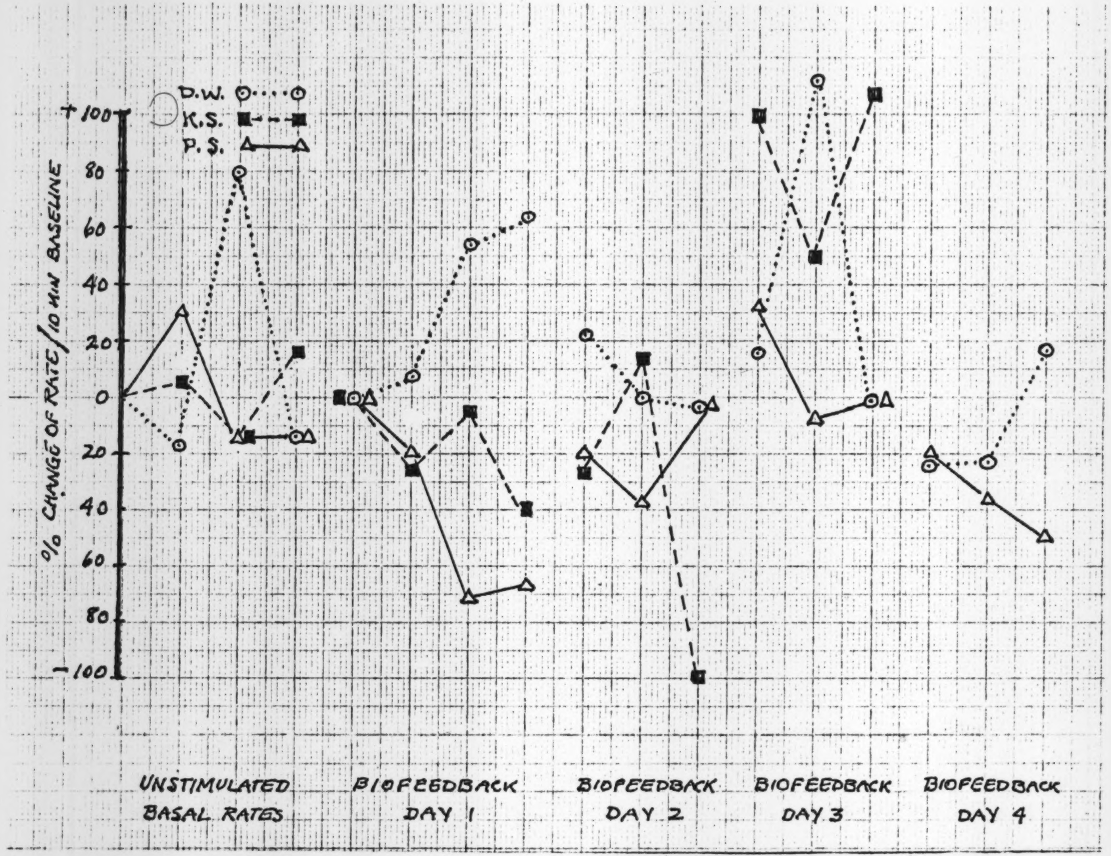

Figure 4.1 Relative rate of acid secretion during all biofeedback trials compared to baseline on each day. Spontaneous changes during comparable periods on unstimulated basal recording day are also shown.

subdivided, inhibition appeared in effect during 40% to 60% of those trials. The degree of control achieved in successful trials was typically around 25% of baseline rate (Table 4.2).

The probability that such an outcome would occur by chance can be estimated by using a simple sign test, assigning a + to a frame whose slope exceeds baseline and a - when it is less. The binomial probability (P_{bin}) for each subject is less than .05, and for the group less than .001.

The results suggest that the three subjects attained various degrees of control in the time alloted: K.S. exhibited the greatest control, including both inhibition and excitation. P.S. showed consistent inhibitory control, and D.W. gave indications on the last day that his usual secretory pattern was yielding to voluntary influences.

The remarks of the subjects were studied for communalities and successful strategies. During the inhibition trials, all subjects mentioned deliberate attempts to relax and concentrate. Several times the strategy of "letting" the secretion decrease, as opposed to "making" it decrease, was mentioned. This was the strategy employed successfully by subject K.S. to completely inhibit acid secretion. Only one subject mentioned the obvious strategy of imagining the dog feces stimulus, which he considered ineffective.

The one subject (K.S.) who reached criterion on the inhibition trials subsequently attempted to increase acidity. On the first day, she was successful, showing increases of 100, 50, and 109% on successive trials, and demonstrating rates above daily baseline on 12/15 three minute frames ($P_{bin} < .02$) (Table 4.3), making further training unnecessary.

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Table 4.2 Regression Coefficients for Final Day of Voluntary Inhibition of Three Subjects. Daily Baseline, Trials and 3-Minute Frames Within Trials Were Analyzed

Subject	Day	Baseline	Trial 1			Trial 2			Trial 3		
		B	B	Frame #	B	B	Frame #	B	B	Frame #	B
D. W.	4	2.500	1.828	1	2.0	1.871	1	1.5	2.846	1	2.0
				2	1.0		2	1.5		2	2.5
				3	2.0		3	2.0		3	3.0
				4	2.5		4	2.0		4	3.5
				5	1.0		5	1.5		5	2.0
K. S.	2	1.066	0.792	1	0.5	1.196	1	0.0	0.000	1	0.0
				2	0.0		2	1.5		2	0.0
				3	1.0		3	1.0		3	0.0
				4	1.0		4	1.5		4	0.0
				5	0.5		5	1.5		5	0.0
P. S.	4	5.516	4.392	1	5.5	3.382	1	0.5	3.746	1	2.5
				2	6.0		2	3.0		2	5.0
				3	2.5		3	2.0		3	6.0
				4	4.5		4	5.0		4	1.0
				5	2.5		5	5.0		5	3.0

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Table 4.3 Gastric Acid Secretion Rates and Percent Changes from Baseline for Subject Rewarded for Increases

		Baseline	Trial 1		Trial 2		Trial 3	
Subject	Day	mEq/min	mEq/min	% change	mEq/min	% change	mEq/min	% change
K. S.	1	.07	.140	100	.106	50	.146	109

The subject remarked at the time of the successful trials that she thought about food, and stressful experiences. She did not believe these were effective strategies, however, and said she did not use them continuously.

Discussion

The results generally support the conclusion of other researchers (Welgan, 1974; Whitehead et al., 1975; Moore & Schenkenberg, 1974) that gastric acid secretion can be modified by instrumental techniques. As has been previously observed (Whitehead et al.), there are great differences in the speed with which individuals attain significant control.

The fact that one subject was able to completely suppress secretion within only 90 minutes of reinforcement and then to effect an increase of more than 100% within 45 minutes of reinforcement, suggests that the biofeedback technique employed can be quite effective in promoting self-control.

These data also suggest that, having learned to control secretion in one direction, a subject is prepared to exert control in the other, and therefore, that the same mechanism is involved in both inhibition and excitation.

When the effects of voluntary cephalic influences are compared to the involuntary responses earlier reported, the magnitude of voluntary inhibition and its duration can exceed its counterpart. The magnitude of voluntary excitation was not tested, but it is not unlikely that, with proper training, it could rival the excitation caused by the sight and smell of food. As would be expected, these voluntary effects require some training. Predictably, the effects would increase in magnitude and reliability over longer training, whereas the involuntary responses would probably decrease with repeated stimulation. As a technique for therapeutically modifying the variability in secretory rate due to vagal influences, the biofeedback technique holds promise.

It was not clear whether voluntary inhibition was followed by a second rebound phase. In the observations of K.S., it appeared to be the case, since a successful effort on the first trial each day was followed by a much less successful trial, followed by a more successful trial--exactly as one would expect if rebound were present. While subject P.S. shows a different pattern from trial to trial, a close inspection of his responses indicated that he was effecting inhibition of a shorter duration, followed by an equally brief increase, so that the net effect of his efforts over a trial was not consistently good. His exceptional performance on the first day was probably due to extreme postural manipulations which were not permitted on subsequent days. With subject D.W., the tendency to increase the rate of secretion after baseline dominated his trials. Only on the last day was there a reliable indication of inhibition, and a possible rebound. In general, it is difficult to see a close similarity between the patterns of secretion during voluntary and involuntary inhibition.

It is also difficult to compare the voluntary excitation of K.S. to the characteristics of involuntary response. In some respects, there is a good fit: two peaks appear in the voluntary response, one (150%) about 10 minutes after beginning the first trial, and a second (200%) about 38 minutes later, with a trough in between. This is roughly the shape observed in the involuntary response, though slower and weaker. No firm conclusions about the relationship of the voluntary and involuntary responses can be drawn from so little data, but it seems plausible that the same mechanisms produce both involuntary and voluntary cephalic influences. If this is the case, the degree of voluntary control possible through biofeedback may equal in magnitude and exceed in reliability the cephalic response effected by alimentary stimuli.

It is interesting to question how subjects control gastric response. From the subjective remarks, inhibition is aided by a relaxed, concentrated state. This state is not unique to voluntary gastric acid inhibition, however, since subjects in other biofeedback experiments have made similar observations regarding a variety of autonomic responses with both sympathetic and parasympathetic dominance. The state may facilitate voluntary inhibition by enhancing autonomic perception and therefore control.

Conspicuously little mention is made of employing the obvious cognitive mediation of imagining disgusting stimuli. Since the sequence of the series of experiments made this strategy so obvious, the reason it was not invoked may have been its intrinsic disagreeableness. A general state of disgust might also have been voluntarily induced without using specific imagery. No one mentioned doing this, either, but D.W., in connection with his successful inhibition trials on the fourth day, commented that he found the experience rather distressing and uncomfortable.

The comments on voluntary excitation strongly suggest cognitive mediation as a strategy, and an effective one. The subject was not convinced that this mediation was important, though, and proceeded to try various other strategies, such as thinking stressful thoughts.

Voluntary control may be viewed as bringing spontaneous fluctuations in acid secretory rate into conformity with some preconceived pattern demanded by the experimenter, by altering their time characteristics and magnitude. Given the complex pattern of the responses to cephalic influences, the patterns demanded by this experiment may have been difficult to achieve. P.S. may have been working with too short a duration, D.W. with too long. More prolonged training may have brought both into closer conformity with the response demands of this experiment. In terms of the day to day variability of secretory rate, P.S. was the most variable, and D.W. the least; K.S. was in the middle. On any day, D.W. and P.S. were about equally variable from trial to trial, and K.S. less so. Such constitutional factors may have a significant effect on training.

A number of questions remain unanswered: What are the limits of voluntary control, excitatory and inhibitory, in terms of magnitude and duration? Does control under these experimental conditions transfer to the normal everyday condition of the stomach? Can a subject learn to modify secretory rate with biofeedback well enough to control it without biofeedback? Since there are obvious individual differences in the ability of this small sample to achieve control, are there subjects who can achieve it faster, perhaps even without feedback, and others who may not be able to modify secretion at all? Perhaps further research will address some of these problems. It now appears to be distinctly possible to answer them.

Summary

In summary, when three normal subjects were given biofeedback reflecting the rate of acid secretion along with periodic quantification of performance and reward, all gave evidence of some degree of ability to alter the secretory pattern in the appropriate manner in a short time.

One subject demonstrated 100% inhibition after six 15 minute trials, and 100% increase in rate within three such trials. The other subjects displayed significant voluntary inhibition within twelve 15 minute trials with biofeedback. The subjective statements revealed no common strategy for inhibition, while excitation of acid was related to employing the classically conditioned association between acid secretion and food.

Chapter 5

CONCLUSION

This paper has presented a series of studies investigating the pattern of gastric acid secretory responses to a variety of cephalic influences. In the course of these studies, several objectives were achieved:

(1) A measurement technique was developed to meet the broad requirements for biofeedback application, namely accuracy, sensitivity, and speed. By intragastric titration it is possible to monitor secretory activity continuously with good sensitivity and accuracy over periods as short as a minute.

(2) With this technique the pattern of acid secretory response to excitatory and inhibitory cephalic influences was closely observed. The visual and olfactory stimuli (food or animal feces) had predictable effects on acid secretory rate. The time course of these effects were probably influenced by non-cephalic gastric, and possibly intestinal, mechanisms. Daily fluctuations in baseline rate observed with this technique were even larger than experimental effects.

(3) The technique is also readily applied to biofeedback training. Preliminary data with three subjects indicate that voluntary control of acid secretory rate is facilitated by biofeedback. The acquisition of increased control may require more extensive training.

The results of other studies of cephalic influences, involuntary and voluntary, are supported by the results obtained with this technique.

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APPENDIX A

Log of Titrations to End Point pH 3.5:$NaCHO_3$ Solutions Against 0.1 N HCl

Date	$\mathring{V}$ HCl (ml)	Molarity	$\mathring{V}$. $NaHCO_3$ (ml)	Molarity*
8/6/74	1.0	0.1 N	1.04	0.096 N
8/16/74	5.0	0.1 N	5.36	0.093 N
8/19/74	5.0	0.1 N	4.30	0.116 N
8/20/74	5.0	0.1 N	4.28	0.117 N
8/26/74	10.0	0.1 N	2.09	0.479 N*
8/27/74	10.0	0.1 N	1.02	0.980 N**
8/30/74	10.0	0.1 N	5.18	0.193 N***
10/8/74	10.0	0.1 N	10.40	0.096 N
10/15/74	10.0	0.1 N	10.80	0.093 N
10/24/74	10.0	0.1 N	10.20	0.098 N
10/28/74	10.0	0.1 N	10.10	0.099 N
11/1/74	10.0	0.1 N	10.10	0.099 N
11/6/74	10.0	0.1 N	9.95	0.101 N
11/7/74	10.0	0.1 N	9.80	0.102 N
11/11/74	10.0	0.1 N	10.10	0.099 N

*The intended molarity for all studies except those marked by asterisks was 0.1 N. The intended molarities during certain preliminary studies were *0.5, **1.0, and ***0.2.

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APPENDIX B

Formulae

1. Smoothing of raw data.

An algorithm for smoothing raw data was devised which would adjust each fifteen second data point (Xn) in terms of all the previously entered data points and some weighting factor x, giving a smoothed data point (Sn). Conceptually,

$$Sn = \frac{(Xn + \alpha)\cdot(Sn-1)}{\alpha + 1} \quad .$$

The actual recursive equation was:

$$Sn = \frac{1}{\alpha + 1}\left[Xn + \left(\frac{\alpha}{\alpha + 1}\right) Xn-1 + \left(\frac{\alpha}{\alpha + 1}\right)^2 Xn-2 + \ldots\right]$$

To choose α, various factors were introduced which would preserve the salient features of the data and minimize the distracting effect of apparently random variability. $\alpha = 7$ did this most satisfactorily.

A causal or antisymmetrical window was chosen, rather than one which would take subsequent scores into account as well, because it could be more easily adapted to electronics for hardware applications in the future.

2. First derivative.

The first derivative, or rate for each fifteen second interval, was calculated by a least-squares quadratic polynomial curve fitting technique including five smoothed data points, two on either side of the point to be calculated and plotted. The coefficients entered were:

-2, -1, 0, 1, 2.

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